Each amendment being supported by the application as filed, the amendments to claims 2, 12, 19, 24, 26, 28, 48 and 50 do not add new matter to the specification.

By this amendment, claims 2, 3, 5-9, 12-14, 19, 24-26, 28, 32-34 and 47-51 are under consideration.

A clean copy of the claims is included for the Examiner's convenience.

II. The Invention.

The present invention is elegant in its simplicity: it is based on the discovery that substituting amino acids in surface accessible portions of allergens reduces the IgE binding to the allergen by a sufficient degree (at least 5%) to provide a better immunotherapeutic protein. The reduced IgE binding renders the protein less susceptible to induce anaphylaxis while eliciting a protective IgG response through a Th1-mediated mechanism.

Allergens are well known (see the specification at page 15, line 2 to page 16, line 15), and constitute perhaps one of the most studied classes of proteins. Structures are known for many members of this class. Allergen use in allergy immunotherapy is also well established (specification, page 3, line 27 *et seq.*). Chemical modification of allergens to render them non-anaphylactic has also been studied (page 6, line 8 to page 7, line 4). Use of isoallergens with 25% sequence differences and mutagenesis of allergens are also well known strategies to avoid anaphylaxis (page 7, line 4 to page 10, line 8).

The present invention represents an advance over these approaches. In this case, a rational modification of surface accessible sites, that has been shown to disrupt IgE binding, yields a therapeutic protein for allergy immunotherapy with reduced anaphylaxis potential. This refined approach, established in specific examples, is easily applied to any allergen, as set forth in the specification and the King Declaration (Declaration of T.P. King submitted April 10,

2002), and as discussed in detail below. To suggest otherwise unjustly denies to the inventors the full scope of their invention.

III. Claim Rejections.

(i) Claims rejected under 35 U.S.C. §112, first paragraph (enablement). Claims 2-14, 16-28, 32-34, 47-49 and 51 have been rejected for lack of enablement because the Examiner contends that the specification does not reasonably enable the full scope of the claims. In response, without conceding the correctness of the Examiner's position, claims 4, 10, 11, 16-18, 20-23 and 27 have been deleted and the remaining claims have been amended to be directed to recombinant allergens from the taxonomic orders *Fagales, Hymenoptera or Dermatophagoides*. Accordingly, claims 2, 3, 5-9, 12-14, 19, 24-26, 28, 32-34 and 47-49 and 51, as amended, are at issue.

Applicants assert that the specification enables the full scope of these claims. The claimed invention is directed to recombinant allergens derived from naturally occurring allergens from the taxonomic orders *Fagales, Hymenoptera or Dermatophagoides* wherein a conserved surface-exposed amino acid is mutated to a non-conserved amino acid, which retains the α-carbon backbone tertiary structure of the naturally occurring allergen and has reduced specific IgE binding compared to the natural allergen. Each of the steps required to make and use the claimed invention can be carried out using the procedures set forth in the instant specification and routine procedures that were well known to those of ordinary skill in the art as of the filing date of the application. Hence, as of the filing date of the application, it was routine to identify homologous allergens, including homologous allergens from the taxonomic orders *Fagales, Hymenoptera or Dermatophagoides*, and identify conserved amino acids in the homologous allergens using commercially available alignment programs (see, e.g., King Declaration at page

4). The specification at pages 24-25, bridging paragraph, sets forth the example of using BLAST to identify sequences homologous to Bet v 1 in GenBank and EMBL databases and aligning these homologous sequences with the CLUSTAL W program. The results of one example of this type of search/alignment is attached at Tab A. The results show that the method allows alignment of *Fagales* allergens Bet v 1, Aln g 1, Car b 1 and Cor a 1. These techniques can be used for the routine identification and alignment homologous sequences for *any* allergen from the taxonomic orders *Fagales, Hymenoptera or Dermatophagoides*. Accordingly, when the application was filed, it would have been routine for one of ordinary skill in the art to identify conserved amino acids for *any* allergen within the taxonomic orders *Fagales, Hymenoptera* or *Dermatophagoides*.

Using techniques set forth in the application and other techniques routine at the time the application was filed, one of ordinary skill in the art would have further been able to determine which of the conserved amino acids identified using the methods described above is a surface-exposed amino acid residue of a B cell epitope. Hence, the specification at page 17, lines 29-31 sets forth that the α-carbon backbone is best determined, either before or after mutagenesis, by x-ray crystallography or NMR, both of which were established, routine technologies when the application was filed. Knowledge of the tertiary structure allows identification of surface-exposed amino acids. Furthermore, following identification of the surface-exposed amino acids of even a *single* member of a family of homologous allergens, the alignment procedures discussed *supra* allow the identification of the conserved surface-exposed amino acids of *any* other homologous allergen. Examples of results of identifying the surface-exposure of amino acids from tertiary structure are enclosed at Tabs B-D respectively for Bet v 1, Der p 2 and Ves v 5. Accordingly, using procedures set forth *supra*, at the time the invention

was filed, one of ordinary skill in the art would have been able to identify surface-exposed amino acids, for example, on a *Fagales* allergen homologous to Bet v 1 (such as those set forth in the alignment at Tab A), or a *Hymenoptera* allergen homologous to Ves v 5 or a *Dermatophagoides* allergen homologous to Der p2. Similarly, at the time the invention was made, using the methods set forth in the specification and other routine methods, one of ordinary skill in the art would have been able to determine the surface-exposed amino acids for *any Fagales, Hymenoptera* or *Dermatophagoides* whose three-dimensional structure was known, and *any* homologous allergen thereof.

The criteria for choosing which amino acids are B-cell epitopes that are to be substituted are set forth in the specification, e.g., at pages 14-15. Using the methods discussed *supra* the amino acid should be identified as being conserved with more than 70% identity in all known homologous proteins within the taxonomic order within which the allergen originates (page 14, lines 22-26) and have a solvent accessibility of at least 20% (page 14, lines 31-32). Furthermore, the substituted amino acid should be located in a conserved patch larger than 400 $Å^2$ (page 14, lines 28-30). Determining the area of a conserved patch on a protein of known tertiary structure was routine at the application was filed (see King Declaration). These methods can used to identify B-cell epitopes on the surface of *any* homologous allergen within a taxonomic order.

The specification further specifies that the mutant amino acid substitution should be a non-conservative substitution at the particular position (paragraph bridging pages 14-15).

Finally, using the guidance contained in the specification, as of the filing date of the application, one of ordinary skill in the art would have been able to determine which amino acid substitutions can be made while preserving the α-carbon backbone tertiary structure of the

naturally occurring allergen while reducing specific IgE binding (indeed, it is unlikely that a single amino acid substitution at a *solvent accessible position* would have any effect on the α-carbon backbone structure, and the Examiner has provided no evidence suggesting otherwise). Hence, the specification sets forth at page 17, lines 29-36 that crystallography, NMR or CD-spectra (all routine techniques) can used to determine conservation of an α-carbon backbone in a recombinant allergen. These techniques could have been used to determine conservation of the α-carbon backbone of *any* recombinant mutant allergen. Lastly, the specification sets forth that IgE binding can be determined using a fluid-phase IgE-inhibition assay using the pool of serum IgE derived from allergic patients (see, e.g., page 34, lines 15-18).

Accordingly, the specification gives extensive guidance that allows one of ordinary skill in the art to determine which conserved amino acids of a homologous allergen from *any* allergen from the taxonomic orders *Fagales, Hymenoptera or Dermatophagoides* should be substituted, which type of substitution was to be made and which substitutions would have the claimed properties of retaining conserved tertiary structure and reduced IgE binding. On the date the application was filed, therefore, the specification gave clear guidance to one of ordinary skill in the art on how to make and use the invention.

Furthermore, using the methods set forth within the four-corners of the specification and techniques well know at the time the application was filed, Applicants have reduced the claimed invention to practice using two unrelated allergens from different taxonomic orders. Accordingly, Applicants have provided working examples of two different recombinant allergens, as claimed. Applicant's success in obtaining these structurally unrelated recombinant mutant allergens from different taxonomic orders coupled with the general applicability of the methods used to obtain them confirms that the specification enables the full scope of the

invention. Again, the Examiner has failed to supply a factual basis to question broad enablement of this approach, or that substantiate the Examiner's failure to accord the King Declaration the weight it deserves. As pointed out above and in the specification, each limitation of the claimed invention is well known, and readily achieved using routine techniques.

In applying the factors set forth in *In re Wands* (858 F2d 731, 8 USPQ2d 1400 (Fed Cir 1988)), the Examiner states that the factors most relevant to the rejection are the scope of the claim, the amount of direction or guidance provided, the unpredictability in the art and the amount of experimentation required to enable one of ordinary skill in the art to practice the claimed invention. Each of these factors is addressed in turn.

Scope of the claims. The claims have been restricted to allergens originating from the taxonomic orders *Fagales, Hymenoptera or Dermatophagoides.* Allergens from these orders have been well known and highly studied among those of ordinary skill in the art. At the time the invention was made, one of ordinary skill would have been able to identify the allergens from these orders, including the three-dimensional structure of allergens from the orders, identify homologous proteins among the allergens and, applying the teachings set forth in the specification to such homologous proteins, identify *any* candidate amino acid for substitution on *any* of the homologous proteins, make the substitution with *any* amino acid not conserved at the position and, having made the substitution, determine which of the substitutions gives rise to mutant allergens that retain the tertiary structure of the native allergen and have reduced IgE binding.

Amount of direction or guidance. Applicants have discussed at length *supra* that the specification gives extensive guidance in identifying and aligning allergen homologues, selecting a surface-exposed amino acid for substitution and which type of substitution is to be

made, determining which mutant allergens bearing a substitution retain the tertiary structure of the original allergen and which mutant allergens have reduced IgE binding, compared to the original allergen.

The particular issues raised by the Examiner are addressed as follows.

The Examiner states that the relationship between the sequences of a protein and its tertiary structure (i.e., its binding activity) are not well understood and are not predictable. This general statement, however, is not applicable to the claimed invention which is based upon comparison of homologous related allergens and wherein at least one the allergens has a known three dimensional structure. The Examiner states further that it is unpredictable which amino acids will tolerate change while retaining tertiary structure and reducing IgE binding. As discussed *supra*, however, using the methods set forth in the specification and other methods well known in the art at the time the application was filed, the tertiary structure and IgE binding of a mutant allergen bearing *any* substitution could have been ascertained directly and predictably.

With regard to a pharmaceutical composition and vaccine comprising a recombinant mutant allergen, it is well accepted that vaccination using allergens from natural sources has an inherent risk of side effects due to allergen specific IgE binding (see specification at page 4, lines 5-13). To overcome the possible side effects associated with allergen vaccines, it has been desirable to produce allergen vaccines with reduced IgE binding (see specification at page 6, line 8 through page 7, line 13). One of ordinary skill in the art would understand that *any* recombinant allergen with native tertiary structure and reduced IgE binding would be superior for use in allergen vaccines, compared to the original allergen. The Examiner has failed to provide any credible evidence to the contrary.

There is no merit to Examiner's statement that "even if IgE binding is reduced by 5% or 10%, there is still a 95% or 90% chance that the mutant allergen could bind IgE and induce anaphylaxis." There is simply no quantitative relationship between the percent reduction in IgE binding and the probability of inducing anaphylaxis. Using the Examiner's method of calculating the probability of inducing anaphylaxis would yield the result that the original allergen, which exhibits 100% percent IgE binding in the assay, would have a 100% chance of binding IgE and inducing anaphylaxis. This is clearly not the case – native allergens are the current standard for allergy immunotherapy, which would hardly be the case if they induced anaphylaxis. It is well known by those of ordinary skill in the art that *any* allergen must be administered at dosages that do not induce severe side effects, such as anaphylaxis. In the present invention, even a 5% rèduction in IgE binding increases the value of the mutant allergen in immunotherapy. The Examiner's unsubstantiated statement cannot be the basis for rejecting the claims.

The other potential adverse affects of using the recombinant allergens cited by the Examiner are similarly not supported by any evidence. They are pure speculation and, in fact, contrary to the results expected when using vaccines comprising the recombinant allergens. There is no evidentiary support or theoretical rationale for the Examiner's assertion that the recombinant mutant allergen may increase IgE production and binding. The claimed recombinant allergens have reduced IgE binding in vitro, as demonstrated in standard assays using IgE from allergen patients, and would be expected to have reduced IgE binding in vivo as well. Nor is there support for the assertion that the recombinant mutant allergen may be inactivated before producing an effect. The claimed recombinant allergens bear one or more point mutations, but retain the tertiary structure of the original allergen. Changes in the gross

physical properties of *any* mutant allergen, compared to the original allergen, e.g., susceptibility to proteolytic degradation or immunological effects, will typically be a function of changes in tertiary structure, e.g., unfolding. The claimed mutant allergens, by contrast, retain the tertiary structure of the original allergen. Accordingly, contrary to the Examiner's contention, the claimed recombinant mutagen allergens would not be expected to be more susceptible to proteolysis and would be expected to retain the ability to elicit allergen specific antibody production.

Finally, the Examiner provides no support for other functional properties "known or unknown" that may make the recombinant mutant allergen unsuitable for in vivo therapeutic use. The Board's ruling in *Ex parte Aggarwal*, 23 USPQ2d 1334 (BPAI 1992) is not applicable to the present case. In *Aggarwal* the Board upheld the rejection of claims to a method of treating tumors with lymphotoxins, citing the examiner's position that tumor treatment is "essentially unpredictable" and the activity of lymphotoxins was "not well understood and not predictable" at the time the invention was made. The Board credited the examiner's reasons why there was a "strong likelihood" that the recombinant lymphotoxin may not be effective due, e.g., to degradation before it reaches the target site. The present case is distinguishable from *Aggarwal*. First, as of the May 31, 1984 priority date of Aggarwal's application, the art of tumor treatment was, in fact, unpredictable. In contrast, when the present invention was filed, preparation of allergen vaccines was widely practiced with many allergens-- the art was highly advanced and predictable. Second, as discussed, the native tertiary structure of the instant recombinant allergens makes it unlikely that they will be subject to degradation or have grossly different immunological properties compared to the original allergens from which they are derived. Third, the treatment claimed in *Aggarwal* required that the lymphotoxin have activity on tumors

that were remote from the site of lymphotoxin administration. The efficacy of treatment would therefore be expected to be related to the half-life of the administered lymphotoxin. In contrast, the half-life in respect to allergens or allergen mutants is not normally considered in the field of allergen vaccines. Half-life measurements are associated with serum level of a drug. Specific allergy vaccines of allergens are exclusively subcutaneous, and target the immunological cells of the skin tissue, where they are further processed. One could argue further, in fact, that the claimed allergen mutants having a reduced affinity for the existing allergen IgE would be likely to persist longer in the tissue, resulting in a sustained release.

Working examples. The specification describes three working examples of mutant allergens of two proteins, from two highly divergent orders. The fact that the methods described were successfully applied the two unrelated allergens shows that the methods described in the specification can be applied successfully to *any* allergen within a homologous class of allergen, based on the three dimensional structure of even a single member of the homologous class.

The Examiner cites Skolnick et al., Attwood and Branden et al. as indicating that further examples are required because it is difficult to predict structure or function from amino acid sequences. Applicants believe respectfully that the Examiner's has misapplied these references to the instant claims. Skolnick et al. and Attwood are directed to general methods of predicting protein structure and function based on sequence. In citing the references, the Examiner has failed to distinguish predictive methods based on different levels of homology between proteins, the complexity of the functional unit to be predicted from the sequence and whether or not a the three dimensional structure is know for a member protein family. Accordingly, the Examiner's casual and generalized statements that Skolnick et al. and Attwood

teach the unpredictability of predicting structure or function from sequence are not applicable to the instant case, where the prediction is based on closely related homologous allergens wherein at least one homologous allergen has had its tertiary structure determined and wherein the "function" to be ascertained is an IgE binding site. Furthermore, the Examiner's selective reading of Branden et al. ignores the section of this reference that is directly pertinent to the claimed invention. In its relevant portion, Branden et al. sets forth that:

> If significant amino acid sequence identity is found with a protein of known crystal structure, a three-dimensional model of the novel protein can be constructed, using computer modeling, on the basis of the sequence alignment and the known three-dimensional structure. This model can then serve as an excellent basis for identifying amino acid residues involved in the active site or in antigenic epitopes, and the model can be used for protein engineering, drug design, or immunological studies. (page 348).

Accordingly, Branden et al. explicitly supports Applicants' position that the specification is enabling with regard to defining B cell epitopes on *any* allergen that is a member of a homologous allergen family wherein the tertiary structure has been determined for even one member of the allergen family.

Nor do the other references cited by the Examiner support the position that the specification fails to enable the claims. Abaza et al.'s teaching that amino acid substitutions outside the protein antigenic site can exert drastic effects on the reactivity of a monoclonal antibody against the site is of limited, if any, relevance. The claims are directed to recombinant mutant allergens with substitutions within an antigenic site. Furthermore, as disclosed in the examples, the recombinant allergens have reduced binding of pooled IgE isolated from allergen patients. This IgE fraction comprises heterogeneous polyclonal antibodies that as a group would be less sensitive to changes removed from an epitope than any one particular monoclonal might

be affected. Finally, Lederman et al.'s teaching that even a single amino acid substitution can ablate the binding of a monoclonal antibody to a protein supports Applicant's position that following the procedures set forth in the specification would enable one of ordinary skill in the art to obtain recombinant allergens with mutations in IgE epitopes that reduce IgE binding.

Predictability in the art. Those of ordinary skill in the art routinely and predictably perform each of the methods required to practice the claimed. More generally, those of ordinary skill in the art predictably formulated vaccines from natural or modified allergens.

Quantity of experimentation necessary. Little or no experimentation is required to enable one of ordinary skill in the art to practice the invention. Each of the steps required to practice the invention were well known and predictable at the time the invention was made, requiring no experimentation. With specific regard to identifying mutant allergens with native tertiary structure and reduced IgE binding, as discussed *supra*, using methods set forth in the specification, it would have been routine for one of ordinary skill in the art to identify *any* mutant allergen with these characteristics. Given the routine nature of the methods, the need to identify successful substitutions that retain tertiary structure of the original allergen and have reduced IgE binding from substitutions that do not have these characteristics is not sufficient to constitute undue experimentation. (*In re Wands*, *supra*, (screening negative hybridomas to find one that makes the desired antibody is not undue experimentation.)) Accordingly, the specification disclosure is sufficient to enable one of ordinary skill in the art to practice the claimed invention.

For the reasons set forth above, Applicants respectfully submit all rejections under 35 U.S.C. § 112, first paragraph for lack of enablement have been addressed and overcome. Reconsideration of the claims and withdrawal of all rejections for lack of enablement under 35 U.S.C. §112, first paragraph is respectfully requested.

(ii) Rejections under 35 U.S.C. §112, first paragraph (written description).

Claims 2-14, 16-28, 32-34, 47-49 and 51 have been rejected for lack of written description. Without conceding the correctness of the Examiner's position, claims 4, 10, 11, 16-18, 20-23 and 27 have been deleted. Claims 2, 3, 5-9, 12-14, 19, 24-26, 28, 32-34 and 47-49 and 51, as amended, are at issue. The rejection is respectfully traversed.

Contrary to the Examiner's position, the written description of the specification establishes that Applicants had possession of a broadly applicable invention of elegant simplicity: by altering an amino acid residue in a determinable position in an allergen, one could reduce IgE binding to the modified allergen, making the modified allergen a better candidate for allergy immunotherapy. Once apprised of this description, the skilled artisan can readily implement the invention in *any* allergen having a known or predictable sequence and structure.

The instant specification provides sufficient written description to inform the skilled artisan that the Applicants were in possession of the claimed invention as a whole at the time the application was filed. As set forth in the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, 1, "Written Description" Requirement (Federal Register/Vol. 66, No. 4, 1099-1111, January 5, 2001) ("Guidelines"), an applicant may show possession of the claimed invention with "complete or partial chemical structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." (Guidelines at page 1106.)

In the instant case, the specification provides a combination of chemical/physical and functional characteristics that show Applicants were in possession of the claimed invention. Hence, the specification at pages 16-17 and 19-20 describes the chemical/physical characteristics

of the recombinant allergens as an allergen having a non-conservative amino acid substitution, wherein the amino acid in the original allergen has greater than 70% identity within known homologous allergens, and which amino acid is at least 20% solvent-accessible and is within a conserved region greater than 400Å^2, and which substitution results in a less than 2Å deviation of the root mean square of the atomic coordinates of the mutant allergen, compared to the original allergen. The physical characteristics of the recombinant allergen are further coupled to and constrained by the functional characteristics that the mutant allergen exhibits reduced IgE binding compared to the original allergen, i.e., the amino acid is part of an IgE epitope.

At the time the application was filed, one of ordinary skill in the art would have understood that the Applicants had possession of the claimed invention-- *any* recombinant allergen bearing a the particular type of surface-exposed amino acid substitution described above that had the tertiary structure of the original allergen and exhibited reduced IgE binding. Accordingly, the specification satisfies the written description requirement for the claimed invention.

Applicants respectfully submit all rejections under 35 U.S.C. §112, first paragraph for lack of written description have been addressed and overcome. Reconsideration of the claims and withdrawal of all written description rejections under 35 U.S.C. §112, first paragraph is respectfully requested.

CONCLUSION

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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PATENT TRADEMARK OFFICE

Docket No: 4305/1E144-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Hans Henrik IPSEN; Michael Dho SPANGFORT; and Jorgen Nedergaard LARSEN

Serial No.: 09/270,910 Art Unit: 1644

Confirmation No.: 3210

Filed: March 16, 1999 Examiner: P. Huynh

For: **NOVEL RECOMBINANT ALLERGENS**

MARK-UP TO AMENDMENT UNDER 37 C.F.R. § 1.111

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

February 27, 2003

Sir:

The accompanying Amendment amends the subject application as follows.

IN THE CLAIMS

Claims 4, 10, 11, 16-18, 20-23 and 27 have been deleted, without prejudice or disclaimer.

Claims 2, 12, 19, 24, 26, 28, 48 and 50 have been amended as follows.

2. (4X Amended) A recombinant allergen according to claim 48, obtainable by

a) identifying amino acid residues in a naturally occurring allergen originating from one of the taxonomic orders *Fagales, Hymenoptera or Dermatophagoides* which are conserved with more than 70% identity in all [known] of the known homologous proteins within the taxonomic order from which said naturally occurring allergen originates;

b) defining at least one patch of conserved amino acid residues being coherently connected over at least 400 $Å^2$ of the surface of the three-dimensional structure of the naturally occurring allergen molecule as defined by having a solvent accessibility of at least 20%, said at least one patch comprising at least one B cell epitope; and

c) substituting at least one amino acid residue in said at least one patch with another non-conservative amino acid, wherein the α-carbon backbone tertiary structure of the allergen molecule is conserved.

12. (Twice Amended) A recombinant allergen according to claim 48 [10], wherein the allergen is derived from a pollen allergen originating from the taxonomic order of *Fagales*[, *Oleales or Pinales*].

19. (Twice Amended) A recombinant allergen according to claim 48 [18], wherein the allergen is derived from a mite inhalation allergen originating from *Dermatophagoides*.

24. (Twice Amended) A recombinant allergen according to claim 48 [23] wherein the allergen is derived from a venom allergen originating from the taxonomic order of *Hymenoptera*.

26. (3X Amended) A recombinant allergen according to claim 24 [23], wherein the allergen is derived from *Ves v 5*.

28. (4X Amended) A recombinant allergen according to claim 26 [25], wherein said allergen has one or more amino acid [the] substitution is selected from the group consisting of

(i) Lys [to Ala] at position 72 of SEQ ID NO: 39 substituted with Ala; and [or from]

(ii) Tyr [to Ala] at position 96 of SEQ ID NO: 39 substituted with Ala.

48. (Twice Amended) A recombinant mutant allergen derived from a naturally occurring allergen originating from one of the taxonomic orders *Fagales, Hymenoptera or Dermatophagoides* in which at least one surface-exposed, amino acid residue of a B cell epitope at a position which is conserved in the amino acid sequences of homologous proteins within the taxonomic order from which the naturally occurring allergen originates, is substituted with an amino acid residue which is not conserved in the same position in the amino acid sequences of homologous proteins within the taxonomic order from which the naturally occurring allergen originates, wherein the α-carbon backbone tertiary structure of the recombinant allergen is conserved as compared with the α-carbon backbone tertiary structure of the naturally occurring allergen, and specific IgE binding to the mutant allergen is reduced compared to the IgE binding to the naturally occurring allergen.

50. (Twice Amended) A recombinant allergen according to claim 14 wherein said allergen has one or more [an] amino acid substitutions selected from the group consisting of:

(i) Thr at position 10 of SEQ ID NO: 37 substituted with Pro;

(ii) Asp at position 25 of SEQ ID NO: 37 substituted with Gly;

(iii) Asn at position 28 of SEQ ID NO: 37 substituted with Thr, and Lys at position 32 of SEQ ID NO: 37 substituted with Gln;

(iv) Glu at position 45 of SEQ ID NO: 37 substituted with Ser;

(v) Asn at position 47 of SEQ ID NO: 37 substituted with Ser;

(vi) Lys at position 55 of SEQ ID NO: 37 substituted with Asn;

(vii) Thr at position 77 of SEQ ID NO: 37 substituted with Ala;

(viii) Pro at position 108 of SEQ ID NO: 37 substituted with Gly; and

(ix) Asn at position 28 of SEQ ID NO: 37 substituted with Thr, Lys at position 32 of SEQ ID NO: 37 substituted with Gln, Glu at position 45 of SEQ ID NO: 37 substituted with Ser and Pro at position 108 of SEQ ID NO: 37 substituted with Gly.